Division of Kidney, Urologic and Hematologic Diseases

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September 2001 Council

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Table of Contents

Initiatives, Expansions or Extensions

5004 PROSPECTIVE COHORT STUDY OF CHRONIC RENAL INSUFFICIENCY (RFA DK-01-005)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-005.html

FY 2002 Action

Move to implementation of a longitudinal prospective study of patients with mild to moderate renal insufficiency. The RFA was issued in FY 2001, and a planning phase funded.

Background

End-stage renal disease (ESRD) is an important medical and public health problem in the U.S. that disproportionately affects racial and ethnic minority groups. The increase in the number of ESRD patients is due mainly to an increase in the number of patients with renal disease caused by diabetes. In patients with ESRD, cardiovascular disease is the leading cause of death, and a better understanding of the risk factors for this disease burden is required before interventions can be evaluated and implemented. While numerous epidemiological studies have been conducted in patients with ESRD leading to improved care and better quality of life, few studies have been performed in patients with chronic renal disease prior to reaching ESRD, during a period of chronic renal insufficiency. Of the small number of studies conducted, all of them have significant methodological shortcomings. Thus, our knowledge about the factors that influence decline in renal function and development of cardiovascular disease in patients with chronic renal insufficiency is rudimentary.

Prospective cohort studies have played an important role in defining risk factors for a wide range of diseases and it is envisioned that data and patient specimens obtained from this cohort study will serve as a national resource for investigations of chronic renal disease and cardiovascular disease.

Research Goals and Scope

The objective of this RFA is to establish a prospective, multi-ethnic, and racial cohort study of approximately 3,000 patients with chronic renal insufficiency to determine the risk factors for rapid decline in renal function and development of cardiovascular disease. Establishing a cohort of patients with chronic renal insufficiency, with cause of renal disease similar to that observed in the U.S. ESRD patient population, and following them prospectively will also provide an opportunity to examine genetic, environmental, behavioral, nutritional, quality of life, and health resource utilization factors in this patient population.

5012 URINARY INCONTINENCE AWARENESS CAMPAIGN

FY 2002 Action

The NIDDK's National Kidney and Urologic Diseases Information Clearinghouse will launch a coordinated information program to reach African American and Hispanic and Latino American women, especially those with diabetes. Easy-to-read and culturally-sensitive publications on bladder control that will be translated into Spanish include *Bladder Control for Women; Exercising Your Pelvic Muscles; Menopause and Bladder Control; Pregnancy, Childbirth, and Bladder Control; Talking to Your Health Care Team About Bladder Control; Your Body's Design for Bladder Control*; and *Your Medicines and Bladder Control*. The NIDDK will also plan and develop additional culturally-sensitive messages and materials, working with public and private partners representing African Americans and Hispanic and Latino Americans to identify additional information needs of patients, families, and physicians. This program is one of NIDDK's initiatives to reduce health disparities in ethnic and racial minority populations.

Background

An estimated 13 million people in the U.S. experience incontinence, but women are affected twice as often as men. Pregnancy and childbirth, menopause, and the structure of the female urinary tract account for this difference, but nerve damage from diabetes—a disease that affects 16 million Americans and disproportionately affects African American and Hispanic populations compared to Caucasians—is also a factor. Women who have diabetes and damage to bladder nerves may not know when the bladder is full, and may have problems controlling the urge to empty the bladder and problems emptying it completely, allowing urine to leak and bacteria to grow more easily in the bladder and kidneys.

Research Goals and Scope

NIDDK will: (1) extend its reach to public and private partners to develop culturally-sensitive materials about approaches to bladder control; (2) attend additional professional meetings at which incontinence publications may be promoted; and (3) will promote the availability of free bladder control information in publications for minority audiences.

5016 POLYCYSTIC KIDNEY DISEASE (PKD) CLINICAL TRIALS NETWORK (RFA DK-01-029)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-029.html

FY 2002 Action

Establish a network to design and implement clinical trials to slow the progressive loss of renal function in PKD. The Network, consisting of a Data Coordinating Center (DCC) and Participating Clinical Centers (PCCs), will develop and execute both pilot and feasibility trials and a large, randomized, controlled clinical trial on blockade of the renin-angiotensin axis in patients with PKD. The RFA was issued in 2001.

Background

PKD is the leading cause of renal disease due to a simple Mendelian defect. The disease is the fourth leading cause of end-stage renal failure in the nation. Previous studies have established typical rates of decline of glomerular filtration rate (GFR) in PKD patients. Nevertheless, through much of the course of PKD, GFR is maintained and detectable decreases in GFR occur relatively late in the natural history of the disorder. The optimal time for interventions, type of interventions, and population appropriate for interventions in patients with PKD have not been identified.

Several approaches to treatment of patients with PKD have achieved varying results. A growing body of evidence supports the value of converting enzyme inhibitors (CEI) as the antihypertensive agent most effective for slowing the progression of kidney disease. Efficacy of these agents was first established for type 1 diabetes mellitus and then type 2. A number of smaller clinical trials and meta-analyses support the effectiveness of these agents for all patients with renal insufficiency and proteinuria. With regard to PKD, however, the data are conflicting. Although one small pilot trial failed to detect benefit, other non-randomized studies have reported large effects. However, treatment of hypertension has not been definitively shown to retard loss of renal function in PKD, and clinical efforts to block the renin/angiotensin/aldosterone system have either not been comprehensive or have only been evaluated in small groups of PKD patients.

Studies have been limited in patients because few centers have a population of suitable PKD patients large enough to participate in long-term, randomized, controlled trials.

A small working group, convened last fall, named study of the effectiveness of CEI as the highest priority clinical study in PKD. This proposal received concept clearance from the DKUHD Sub-Council at its February meeting.

Research Goals and Scope

A Data Coordinating Center (DCC) and Participating Clinical Centers (PCCs) will be formed to design, develop, and implement randomized clinical treatment trials for patients with PKD. The aim will be to recruit at least 2,000 patients.

5017 HEMATOPOIETIC CELL LINEAGE GENOME ANATOMY PROJECTS (HCLGAP) (RFA DK-02-018)

FY 2002 Action
Create a consortium of investigators to provide a comprehensive delineation of the patterns of gene expression during hematopoietic differentiation.

Background
Hematopoiesis is an evolutionarily conserved process that can be studied more easily than lineage differentiation in other organs because of the accessibility of the cells; study of hematopoiesis has led to much of the basic science of stem cell biology. The gold standard for the measurement of stem cell activity is the capability of both short-term and long-term repopulation of a lethally irradiated animal, but other surrogate assays have been useful. Purification of hematopoietic stem cells through the use of monoclonal antibodies has been accomplished, however imperfectly, and lineage-specific progenitors have been purified recently. In addition, recent studies have demonstrated the plasticity of stem cell populations within individual organs. The marrow contains stem cells that are committed to hematopoiesis as well as stem cells that are mesenchymal in origin. These stem cells can be driven to a large number of tissues with exogenous factors. Although the process is relatively inefficient *in vitro*, contribution of marrow cells to non-hematopoietic lineages has been documented *in vivo*. Thus, the marrow may represent an undifferentiated tissue that was derived during embryogenesis and that can maintain highly plastic stem cell populations from diverse tissues and possibly may be used to derive any organ.

The Trans-NIDDK Stem Cell and Developmental Biology Working Group recently drafted a set of recommendations for stimulating research in this area. The recommendations included establishment of a systematic process to assess gene expression throughout differentiation. This process would be the catalyst for a nationwide effort to characterize the molecular and cellular features of stem cells. Such an analysis should provide not only entirely new strategies for repairing or replacing damaged organs in individuals of all ages, but also new insights about pathologic processes underlying disordered development, disordered maintenance, and neoplastic transformation of these organs.

Research Goals and Scope
The NIDDK will invite Cooperative Agreement Applications for Hematopoietic Cell Lineage Genome Anatomy Projects (HCLGAP) that will participate in the discovery of the processes necessary for the self-renewal and differentiation of hematopoietic stem cells (HSCs) in health and disease. The specific goals of the projects will be to develop the necessary biological procedures and reagents for characterization of adult HSCs and to characterize gene expression patterns in these cells using advanced technologies and bioinformatics techniques. The focus of the projects will be on intensifying investigator-initiated research, attracting new investigators into the field, encouraging interdisciplinary approaches to research in this area, fostering the application of basic research to generate new research tools and approaches for the study of HSCs, and establishing a comprehensive searchable database. Because of the nature of the research questions, potential applicants will include investigators with expertise in the biology of

progenitor cells, genomics experts, and investigators having substantial expertise in bioinformatics.

The components of each genome anatomy project (GAP) will work together as a consortium. The consortium will serve as a resource to provide reagents and databases that will be made available to the research community. Through the HCLGAPs, individual grantees will have access to information, resources, technologies, expertise, and reagents that are beyond the scope of any single research effort. HCLGAPs also will be expected to collaborate closely with existing NIDDK GAPs in other systems as well as the GAPs funded under a related RFA, to be released concurrently with this one.

5018 MINIMALLY INVASIVE SURGICAL THERAPIES TREATMENT CONSORTIUM FOR BENIGN PROSTATIC HYPERPLASIA (RFA DK-01-024)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-024.html

FY 2002 Action

Establish a group of collaborative Prostate Evaluation and Treatment Centers (PETCs) and a Biostatistical Coordinating Center (BCC) to develop and conduct randomized, controlled clinical trials on the long-term efficacy and safety of major "minimally-invasive" therapies for symptomatic BPH. The RFA was issued in FY 2001.

Background

The DKUHD of the NIDDK has a substantial and longstanding interest in evaluating the effectiveness of treatment strategies for symptoms of benign prostatic hyperplasia (BPH). For many years, transurethral resection of the prostate (TURP) has been the standard of surgical therapy for symptomatic BPH. During the past decade, a number of technical innovations have allowed the development of new surgical treatments, which aim to achieve the same long-term outcomes of TURP but with less morbidity, lower costs, shorter length of hospital stay, and more rapid recovery. These new, "minimally-invasive" surgical approaches include laser therapy, hyperthermia and thermotherapy, transurethral electrovaporization, microwave therapy, and transurethral needle ablation. Other new techniques are appearing regularly. The outcomes of these minimally invasive therapies are uncertain. Published studies suffer from a lack of uniform outcome measurements, variable baseline or study entry criteria, a short period of follow-up, lack of information on the frequency of re-operation, inadequate documentation of adverse events, and absence of information on post-surgical pharmacological treatment.

Research Goals and Scope

The purpose of this RFA is to solicit applications from centers that will serve either as a data-coordinating center or a clinical center. These centers will participate in a consortium that will develop and conduct randomized controlled clinical trials to evaluate the long-term efficacy and safety of the most frequently used "minimally invasive" surgical approaches for the treatment of symptomatic BPH. The primary objective of this RFA is to develop and carry out clinical trials, singly or concurrently, to evaluate the long-term efficacy and safety of these devices. The cooperative group of investigators, to be known as the Minimally Invasive Surgical Therapy (MIST) Study Group, will also develop objective diagnostic and outcome measures. Trials may focus on comparisons of a single surgical technique with a sham control or on comparisons of multiple techniques with each other and sham controls. Comparisons with medical therapy may also be considered. PETCs will require expertise in urology and experience in conducting multi-center clinical trials related to the treatment of BPH. The BCC must have expertise in biostatistics, data management, database development, and computer programming, as well as experience in coordinating multi-center clinical trials or epidemiological studies.

5019 FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS) IN CHILDREN AND YOUNG ADULTS INTERVENTIONAL STUDY (RFA DK-02-013)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-013.html

FY 2002 Action

Create a network to test the value of selected immunosuppressive interventions with converting enzyme inhibitors as an adjuvant intervention for preventing progression of FSGS in children and young adults. An RFA was issued in FY 2001.

Background

FSGS is a common, irreversible process that results in steroid-resistant nephrotic syndrome. It often appears as a primary condition, with a propensity for an unfavorable outcome—risk of progression to end-stage renal disease (ESRD). FSGS is one of the most common recurrent diseases post transplant in children, resulting in allograft injury (20 to 30 percent), or graft loss (40 to 50 percent). The peak incidence is in pre-school age children, with males more often affected (2:1). The worst prognosis is observed in African American children. Steroid therapy (i.e., prednisolone or, lately, deflazacort) has been used to treat children with FSGS; the response is unpredictable. Limited data suggest that alternative therapy with alkylating agents (i.e., cyclophosphamide or chlorambucil) or with immunosuppressive agents (i.e., levamisole or CsA) may be beneficial in reducing relapses, reducing proteinuria, and perhaps arresting disease progression.

Non-selective proteinuria, ascribed as contributing to tubulointerstitial damage and progression of renal disease, is considered both a marker of glomerular injury and a risk factor for progression. The localization of the gene for the rare inherited type of FSGS to *1q25-q31* has helped to define one distinct subset of the disease.

A task force to gather information on the criteria for, and nature of, interventions for a clinical trial was convened jointly by the NIDDK and the American Society of Pediatric Nephrology in November 2000. This initiative is based on the recommendations of this group.

Research Goals and Scope

A prospective, randomized, multi-center clinical trial examining the impact of immunomodulatory therapy on proteinuria is proposed. The needed sample size is estimated at approximately 300 patients enrolled over a three-year period and followed for approximately 24 months. If successful, the results of the clinical trial will guide physicians in providing the safest and most efficient care for children with FSGS.

5025 DATABASE AND REGISTRY FOR GENETIC RENAL AND GENITOURINARY DISEASES

FY 2002 Action
Create a registry of well-characterized pediatric urology and nephrology patients with single-gene disorders that can be accessed by qualified investigators for approved basic and clinical studies.

Background
Monogenic disorders of the renal and genitourinary systems are not common. Development of a central registry will allow accumulation of information on patients with these disorders, information necessary for conducting scientific and clinical studies of statistical relevance and significance. This concept was developed from the Pediatric Nephrology Strategic Plan.

Research Goals and Scope
Using the contract mechanism, a contractor will be designated to assume the duties of managing the database. On a pilot basis, beginning with hyperoxalosis and recessive polycystic kidney disease, a working group will be formed to establish procedures and a common consent protocol and to address the confidentiality and sharing issues. If a satisfactory model is developed, the scope of work of the contract could be widened to include other conditions.

5026 EFFICACY OF PHYTOTHERAPY FOR TREATMENT OF BENIGN PROSTATIC HYPERTROPHY (BPH)

FY 2002 Action
Establish a trial network to determine the safety and efficacy of widely used herbal supplements to treat benign prostatic hypertrophy.

Background
More than 50 percent of men 50 years of age or older have symptoms attributable to BPH. BPH has been shown to have a significant negative impact on patient-reported quality of life and psychological well-being. BPH treatment accounts for at least 1.7 million office visits per year, and the costs associated with treatment of this condition have been estimated to exceed $4 billion per year. The symptoms commonly associated with BPH have become a major target for alternative therapeutic approaches. A recent survey has shown that in selected clinical practices up to 90 percent of men are either using or have used alternative medicine to treat BPH symptoms. A recent editorial in the *New England Journal of Medicine* highlighted the need for further testing of herbal remedies. The editorial concluded, "Alternative therapies should be subjected to scientific testing no less rigorous than that required for conventional treatments." Phytotherapy for BPH involves predominantly one of two different plant-derived agents: *Pygeum africanum* or saw palmetto berry. No reliable published information is available about: (1) the effects of these agents on prostate pathology; (2) the safety of these therapies; (3) their systemic effects; or (4) their optimal dosages. An *ad hoc* BPH phytotherapy advisory group convened by the DKUHD recommended establishment of the trial network to determine the safety and efficacy of these phytotherapies in treating BPH.

Research Goals and Scope
A trial network will be established with experts in clinical trials on benign prostatic hypertrophy. The network will design and implement full-scale efficacy studies of one or more herbal agents widely used for treatment of prostatic symptoms.

5027 CLINICAL TRIAL OF SAW PALMETTO AND BPH

FY 2002 Action

The purpose of this initiative is to develop, in collaboration with the National Center for Complementary and Alternative Medicine (NCCAM), a multicenter study designed to evaluate and compare alternative medical and approved pharmacological approaches, alone and in combination for effective treatment of BPH. Because claims for these agents are also being made for prostate cancer, input and advice from investigators studying prostate cancer will also be sought.

Background

Phytotherapy and other alternative medicines are widely used approaches to the treatment of symptomatic BPH. Their efficacy has never been studied. The two major phytotherapies, saw palmetto and *Pygeum africanum*, are very widely used for BPH treatment in the U.S., Europe and Asia. Many traditional physicians suggest that the effect is purely placebo; however, others suggest that the treatment is efficacious but the method of action is not known. It is essential that these agents be studied and compared with conventional therapy so that physicians can adequately advise and treat patients with the most effective therapy for the defined symptoms and pathology. A small pilot trial of saw palmetto, co-funded with NCCAM is currently under way.

5028 CLINICAL TRIAL OF DAILY DIALYSIS

FY 2002 Action
Develop a pilot and feasibility study to rigorously assess the impact of more frequent dialysis on objective measures of patient well-being.

Background
The clearance of toxic compounds by hemodialysis depends upon the blood level of the compound in question, duration of dialysis, blood-flow rate, and dialyzer membrane characteristics. In general, observational studies have identified a broad correlation between better outcomes and more intensive dialysis. The NIDDK currently supports a large randomized trial (HEMO) of hemodialysis patients. The HEMO trial examines the impact on mortality of increasing dialysis dose by increasing time or membrane surface area. The study also compares the impact of high flux dialyzers on patient outcomes. The HEMO trial will end in FY 2002, and results will be available to guide the planning process for subsequent trials in this population.

During the last year, the renal community has developed a strong interest in the potential of intensified dialysis regimens, either slow nocturnal or short daily dialysis, to improve patient outcomes. Increasing dialysis frequency has a number of theoretical advantages as a strategy to improve dialysis dose, since clearance of accumulated toxins is greatest early in a dialysis run. In a small number of sites, with highly selected patient groups, markedly improved patient rehabilitation, better control of plasma phosphate, and reduced Epogen requirements have been reported with more frequent dialysis. In collaboration with the Health Care Financing Administration (HCFA), the NIDDK organized an intensive two-day planning meeting of dialysis experts to explore the feasibility of a randomized trial of these new treatment strategies. Data in support of this new treatment approach were reviewed. Proposals were presented for trials of both nocturnal dialysis and short daily in-center dialysis.

Experts at the meeting were in general strongly supportive of the need for careful evaluation of these new therapeutic approaches. The feasibility of a randomized trial was discussed extensively; although a number of concerns were raised, most meeting participants were strongly supportive of the need for the kind of rigorous evaluation only possible with randomized participants.

Recommendations from the Daily Dialysis Workshop on April 11 and 12, 2001, supported the implementation of a carefully designed randomized trial of frequent dialysis. NIDDK and HCFA are exploring the feasibility of arrangements that, in the context of a trial, would allow reimbursement of the additional care costs, under a HCFA waiver.

Research Goals and Scope
Preliminary studies will be implemented through the HEMO trial network to assess the feasibility of implementation of daily in-center dialysis into the operation of standard in-center dialysis care, to assess clinical management strategies for patients on daily dialysis, and kinetic modeling of dialysis efficiency in the setting of more frequent dialysis. These studies, plus the results anticipated from the HEMO trial will guide

development of trial strategies to determine the patient benefit of more intensive dialysis regimens.

5030 KIDNEY/GENITOURINARY GENOMICS TOOLS

FY 2002 Action
Create a consortium of investigators to support the development of a set of genomics tools that will be useful for the study of diabetic nephropathy and other kidney diseases and for study of urologic disorders.

Background
Comprehensive descriptive databases of the changed patterns of gene expression and protein abundance during the development of the genitourinary tract and during progression of important kidney and urologic disorders would be valuable resources for a variety of types of research being supported by the Institute. Such data will be useful for gene finding studies and for studies attempting to develop better animal models. This data would also be a resource for investigator-initiated grants exploring specific gene pathways to understand pathogenesis, to use as therapeutic targets, or to use as novel markers of disease. Progress in application of genomics in kidney, prostate, and bladder research in health and disease is hampered by extreme anatomical and cellular heterogeneity of the kidney and the genitourinary tract and by incomplete knowledge of the important genes that are active or inactive during disease. The MGC databases do not include many kidney and bladder genes from non-cancerous tissues. Both normal and cancerous prostate tissues have been extensively included in CGAP, but application of this information in the study of non-cancer diseases or disorders has been slow. Therefore, determining what genes are active in normal tissues and how these genes change with disease is of great interest. In addition, the role of stem cells and the interrelationships between cellular components in bladder and prostate physiology is poorly understood. Identification of these changes will permit the development of both new therapeutic targets and clinical profiles that will allow identification of patients at risk for kidney, prostate, or bladder disease.

Research Goals and Scope
This initiative will support the development of the following:

- Integrated bioinformatics websites that would facilitate access to existing genomics tools and contribute to increased awareness of genomics resources for disease investigation. The website would track and list known kidney, prostate, and bladder genes, with links to large datasets (IMAGE, MGC, RIKEN, etc). The site would use innovative topological methods to display gene expression data.
- A gene-finding component that would develop cDNA libraries and full-length cDNA clones in expression vectors suitable for protein expression and two hybrid studies. Novel gene-finding strategies would be employed to search for genes not currently in MGC that are expressed under abnormal conditions. All genes should be displayed on the bioinformatics website and distributed freely to the research community.
- Tools to address the special needs posed by the spatial and cellular complexity of the kidney, prostate and bladder. This would include technology development to allow use of genomic/proteomic techniques in rare compartments and in clinical samples, including methods to acquire material from archival samples, laser

capture microdissection, optimization of RNA amplification, enhancing signal detection, and microassays for protein abundance and function.

- Tools for systemic assessment of gene expression, transgenic and tissue/cell specific knockout mice, and phage display antibodies to organ-specific proteins and cell types.
- A national repository for prostate, bladder, and kidney tissue; biological fluids; and clinical data from patients who undergo surgical resection or biopsy of these organs. The purpose of the proposed initiative is to stimulate cooperative efforts to identify and improve access to these tissues, biological specimens, and associated clinical outcome data, which could then be used by the research community at-large for research on the pathogenesis of disease and development of more effective therapies.

5031 PROSTATE RESEARCH NET (NOVEL EXPLORATORY TEAMS)

FY 2002 Action
Issue a solicitation to expand the pool of prostate researchers and to increase the use of novel technologies and innovative approaches in prostate research.

Background
Diseases of the prostate affect 2.8 million men in the U.S. These diseases include prostate cancer, which will be diagnosed in 180,400 men this year and will kill over 31,000 men; benign prostatic hypertrophy, which affects nearly 1 out of 2 men over the age of 50; and prostatitis. These disorders contribute significantly to medical costs, doctor visits, and a reduction in the quality of life for sufferers.

Basic science research on prostatic diseases has rapidly progressed over the past several years. However, progress and approaches have been constrained by the limited number of investigators in this field. The complexities of prostate research impede entry of new investigators from outside the field. Frequently, new investigators lack insight and materials to develop rigorous prostate research programs.

The FY 2002 action is the result of the following information-gathering and planning meetings: the NCI-sponsored Prostate Research Progress Review Group, April 1997; the International Symposium on Prostate Growth, March 1998; and the Symposium on Prostate Growth and Aging, September 13-15, 2000.

Research Goals and Scope
The goals of the Prostate Research Novel Exploratory Teams (Prostate Research NET) would be to expand the number of investigators in the field and to introduce novel research technologies and approaches to the field. The Prostate Research NET would utilize the exploratory (R21) grant mechanism and would require the teaming of an established prostate researcher with a researcher from another field or a new investigator. These teams would utilize a novel combined approach to a problem in prostate research.

5033 SEMEN IN TRANSMISSION OF HIV

FY 2002 Action
Study the mechanisms of semen transmission of HIV and develop strategies for prevention of semen transmission.

Background
HIV in semen is one the major factors in the development of the AIDS epidemic. Sexual contact with HIV seropositive men is a major route for transmission of HIV. Sources of HIV transmission in semen have been identified as both the free virus particles and infected cells. Confounding factors in the study of the biology of HIV in semen are the limited knowledge of the relationship among systemic host factors, the levels of potentially infectious HIV in the semen, and the immunology of the male urogenital tract. The anatomical origins and sources of HIV in the male genital tract have not been positively identified; neither have the effects of therapeutic interventions on HIV infectivity.

This initiative is the outcome of a planning meeting convened in spring 2000 to review the state of knowledge and to develop a research plan.

Research Goals and Scope
The purpose of this initiative is to develop studies that will elucidate factors determining HIV transmission and shedding in the male genital tract. Other important research areas include: (1) elucidation of HIV infectivity in semen fractions; (2) relationship between the immunobiology of the male genital tract and HIV replication and infectivity; and (3) factors that influence HIV transmission through semen, such as genital tract inflammation.

5035 HOMOCYSTEINE-LOWERING TRIAL IN RENAL TRANSPLANT PATIENTS

FY 2002 Action
Plan and conduct a large simple trial to determine whether lowering homocysteine levels with folate and B vitamin supplementation reduces cardiovascular mortality in renal transplant patients.

Background
A very sizable body of correlative data suggests that elevation of homocysteine levels causes premature atherosclerotic disease; however, data supporting the inference that lowering homocysteine will reduce risk is sparse. Patients with renal insufficiency demonstrate both elevated homocysteine levels and markedly enhanced cardiovascular disease risk. Interventions to lower homocysteine are of documented effectiveness in this population, and because homocysteine levels are higher than in the general population, the effects of folate fortification of flour are less problematic. The renal transplant patient group offers a number of advantages for interventional trials; sizable populations of patients are followed usually yearly by large transplant centers, facilitating cost-effective patient recruitment. Patients are generally compliant and many have participated in trials in the past.

Research Goals and Scope
A large investigator-initiated R01 (PI-Andrew Bostom) was funded in FY 2001 to begin the planning phase of an interventional trial on this question. This proposal has been converted to a U01, and an external advisory committee has been established. The final protocol will be reviewed by NIDDK and the External Advisory Committee early in FY 2002, and assuming the trial design is approved, the trial will move forward to full implementation in FY 2002. The trial will require patient follow-up for five years.

5036 AASK COHORT STUDY (CONTINUATION OF AASK COHORT)

FY 2002 Action
Investigate the environmental, socio-economic, genetic, physiologic, and other co-morbid factors that influence progression of kidney disease in a well-characterized cohort of African Americans with hypertensive kidney disease.

Background
African Americans are disproportionately afflicted with end-stage renal disease (ESRD). They constitute approximately 12 percent of the U.S. population but comprise 32 percent of the prevalent ESRD population. Diabetes mellitus is the predominant cause of ESRD in the U.S. population. In African Americans, especially, hypertension is a major cause of ESRD. In 1990, the NIDDK launched an initiative to investigate the underlying cause of hypertensive kidney disease and to study mechanisms that could slow its progression in African Americans. The clinical trial, "African American Study of Kidney Disease and Hypertension" (AASK), was initiated to investigate whether a specific class of antihypertensive agents (beta-adrenergic blockers, calcium channel blockers, or angiotensin converting enzyme inhibitors), and/or the level of blood pressure (mean arterial pressure [MAP] of 102-107 mm Hg or MAP of 92 mm Hg) would influence progression of hypertensive kidney disease in African Americans.

After a brief pilot study (1992-1994), 20 clinical centers and a data coordinating center were funded to carry out the full-scale clinical trial in 1994. The 21st clinical center was added in June 1996. As in the pilot clinical trial, all four historically black medical schools are funded to participate in the full-scale trial. The centers required nine months to revise the protocol for the full-scale trial, and participant recruitment and randomization began in April 1995. The intervention component is scheduled to end in March 2002, and the primary analysis of the study results to conclude in June 2002. The cohort study will commence at the conclusion of the intervention study. The investigators at the clinical and data coordinating centers and the program staff at the NIDDK have been meeting and discussing the format of the "After-AASK" Cohort Study during the past three months. The team will complete design of the study within the next four months.

Research Goals and Scope
The AASK cohort will continue to be followed at the clinical centers; however, some patients at centers with a small number of participants will be followed at a nearby larger participating center. In some instances, some of the smaller centers may be asked to recruit additional African Americans with hypertensive kidney disease to augment the patient population at the center. The patients will be provided with the usual clinical care given to all such patients at the respective centers. Baseline demographic information, selected laboratory tests, and other studies will be obtained at the initiation of the Cohort Study. Patients will be seen quarterly at the centers, and some selected studies will be done at these visits. Samples will be obtained and stored for additional studies and analyses at a later date. The protocol used in the AASK Cohort Study will be similar to that proposed for the new Chronic Renal Insufficiency Cohort (CRIC) study to be initiated by mid- to late 2002 to permit ultimate integration and comparison of the two data sets.

5037 HEMO EXTENSION

FY 2002 Action

Extend study three months to enable complete, planned follow-up of all participants. This action is necessary because the recruitment phase of HEMO was extended three months to meet recruitment goals. No continuation phase of HEMO is planned.

5038 CHRONIC PROSTATITIS COLLABORATIVE RESEARCH NETWORK

FY 2002 Action
Extend studies one year.

Background
The Chronic Prostatitis Collaborative Research Network has undertaken three types of studies—basic laboratory investigation, a longitudinal cohort study, and a randomized clinical trial. The trial group began implementing the clinical trial during the past year, and the final extension year for this consortium is needed to complete this aspect of the project. Two additional sites were added in the past year to facilitate minority recruitment. Full-scale implementation of trials with all sites recruiting would occur in FY 2002. Full implementation of these trials has been an on-going item of Congressional interest.

5039 PRECLINICAL TOXICOLOGY OF IRON CHELATING COMPOUNDS

FY 2002 Action
Establish a mechanism for toxicology testing of iron chelator compounds.

Background
The "Cooley's Anemia Control Act of 1972" authorized grants and contracts for basic and applied research on Cooley's anemia. To carry out this mandate, the NIH Inter-Institute Coordinating Committee for Cooley's Anemia determined that development of an effective iron-chelating drug was feasible and of the highest priority. The urgency was based on the following facts:

- Morbidity and mortality of patients with Cooley's anemia is due primarily to the deposit of large amounts of iron in tissues (heart, liver, kidneys), arising from chronic transfusions patients must receive in order to remain alive.
- Patients maintained on regular transfusions are relatively healthy until iron deposits begin to produce symptoms of heart and liver failure.
- An iron-chelating drug is in clinical use (DesferalR), but it is expensive, is not effective orally, and must be administered parenterally *via* a pump, over a 12-hour period daily.

Since 1972, on the recommendation of the Inter-Institute Committee, the NIDDK has assumed the lead role in developing new iron-chelating compounds and in testing them for efficacy and toxicity. During this period, several hundred compounds have been screened for efficacy in iron removal from test animals, and five of the most promising have been evaluated for toxicity. Within the past 24 months, preclinical toxicologic studies, under a single NIDDK contract have investigated a parenterally effective iron-chelating compound. These studies are designed to support an Investigational New Drug Application (IND) for clinical trials by a pharmaceutical company to determine the safety and efficacy of the compounds. Other investigators are performing toxicologic studies on additional compounds under independent support.

A workshop entitled "Iron: From Current Biochemistry to New Chelator Development Strategies" was held in the Lister Hill Auditorium at NIH on September 21 and 22, 1998. Its purpose was to examine the status of iron chelation development and to consider new means to control iron accumulation in patients. Workshop participants enthusiastically supported a continued search for new chelating drugs. The workshop was followed by an RFA resulting in 13 grant awards by the NIDDK and National Heart, Lung and Blood Institute. Several of the awards are devoted to new chelator development. An RFA grantees meeting was held in Bethesda on April 26, 2001.

Research Goals and Scope
The RFP would identify a contractor to continue preclinical toxicologic evaluation of new candidate chelating drugs. These evaluations are expected to identify promising candidate drugs, and pharmaceutical partners will assume responsibility for toxicologic studies for Phase I, II, and III clinical trials. It is possible that the NIDDK would conduct certain additional studies needed to obtain information supporting these clinical trials. Without this contract, there would be no other mechanism for testing candidate iron-chelating drugs, since these are considered to be orphan drugs.

5040 MEDICAL THERAPY OF PROSTATIC SYMPTOMS (MTOPS) BASIC SCIENCE CONSORTIUM (RFA DK-02-017)

FY 2002 Action
Identify and evaluate biomarkers associated with, or predictive of, the development of benign prostatic hypertrophy (BPH), prostate cancer, and/or response to two medical BPH treatments (finasteride and doxazosin) included in the MTOPS trial.

Background
Benign prostatic hypertrophy (BPH) affects more than 50 percent of men past the age of 50. BPH is an expensive disease. BPH treatments cost an estimated $5 billion each year, and as the U.S. population ages, these costs will increase. If left untreated, BPH can lead to urinary tract infections, urinary retention, and, in rare cases, kidney disease. BPH is a heterogeneous disorder, with growth occurring in different portions of the gland. Both clinical presentation and responses to treatment are mixed. Furthermore, although there is no clear link between BPH and prostate cancer, these two prostate diseases occur in a similar population of aging men. NIDDK has sponsored a large clinical trial of two treatments for BPH, finasteride and doxazosin. This trial, entitled "Medical Therapy of Prostatic Symptoms" or MTOPS, included acquisition and storage of prostate biopsies from participants as they entered and exited the trial. These samples will allow the development and evaluation of potential biomarkers for BPH, prostate cancer, and response to BPH treatments.

Several meetings were held to assist the planning process: the NCI-sponsored Prostate Research Progress Review Group, April 1997; the International Symposium on Prostate Growth, March 1998; and the Symposium on Prostate Growth and Aging, September 13 to 15, 2000. MTOPS Meetings were held October 12, 2000, and February 8, 2001 (tissue subcommittee).

Research Goals and Scope
An extensive NIDDK-supported clinical trial on Medical Therapies of Prostatic Symptoms (MTOPS) is nearing completion. Part of this study included collection of a variety of biologic samples. The availability of these materials presents an extraordinary opportunity to develop and evaluate biological and genetic markers that will further our understanding of biologic and genetic processes contributing to BPH or related to response to therapy of BPH. This initiative would support creation of a consortium with a range of expertise to perform cooperative studies using this material to evaluate genetic, immunologic, or biochemical biomarkers relevant to the progression of BPH, response to therapy, and the development of malignancy. Follow-up of the MTOPS consortium by questionnaire and/or death certificate analysis will be performed.

5041 VASCULAR ACCESS TRIALS CONSORTIUM

FY 2002 Action
Supplement funding to permit two or three additional recruitment sites and blood flow monitoring.

Background
To perform hemodialysis, establishing a means for recurrent large-bore needle access to the circulation by placement of a graft or fistula is necessary. Complications due to poor function of the vascular access are a major factor in health care costs for dialysis patients. In FY 2000, NIDDK established a consortium of investigators to undertake interventional clinical trials to improve outcomes with fistulas and grafts. In the planning phase, which is just now being completed, the protocol development and sample size calculations have established the need for two or three additional high-volume recruitment sites. Additional funds are also needed for blood flow monitoring, which will be important in ascertaining the primary endpoint.

5042 MINORITY ORGAN AND TISSUE DONATION PROGRAM (RFA DK-02-019)

FY 2002 Action
Increase the number of organs and tissue donated for transplantation in racial and ethnic minority communities.

Background
Racial and ethnic minorities, particularly African Americans, American Indians, Alaskan Natives, and Hispanic Americans, are disproportionately afflicted with end-stage renal disease (ESRD). Although transplantation is the preferred renal replacement therapy because it improves survival and quality of life for successful transplant recipients, these racial and ethnic minority groups are less often transplanted. A frequently cited reason is that the organ donation rate for minority groups is much lower than their representation in the ESRD patient population. With an increased number of organs from minority groups in the pool, there would be a better match, and ultimately, better graft survival for minority patients.

Over the past five to eight years, several programs have been initiated to increase organ and tissue donation in minority groups. The NCMHD/NIDDK-funded MOTTEP program was established, in which intensive educational and information activities have occurred in 15 cities across the U.S. During the same period, the Department of Health and Human Services intensified educational and information programs throughout the U.S. through the Organ and Tissue Donation initiative. Perhaps as the result of these combined efforts, organ and tissue donation has increased, especially in the minority communities. However, the rate of organ and tissue donation from minorities is lower than their representation in the population with organ failure, especially ESRD. By increasing the educational activities in other minority communities, this will enhance minority organs in the pool, and hence increase the chances of a better match and improved graft survival.

Several potential grantees have been in contact with NIDDK program directors and have expressed their wishes to participate in the educational process, especially in minority communities.

Research Goals and Scope
The purpose of this initiative is to create an environment supportive of organ donation by

- Increasing exposure to donation messages and to opportunities to express donation commitments. This could be accomplished through increasing exposure in national and local media; increasing community interventions (at schools, churches, etc.); increasing promotion of organ donation through health promotion and disease prevention efforts; and disseminating and replicating best practices identified through research and evaluation.
- Evaluating the impact of increased support for living organ donation (e.g., provisions to cover child care, travel, and other expenses for living donors).
- Increasing minority cadaveric and living organ donation.
- Increasing donation from non-traditional donors (e.g., older donors and living donors).

DIVISION OF KIDNEY, UROLOGIC, AND HEMATOLOGIC DISEASES
Conferences and Workshops

Planning a Research Career in Urology
Organizers: Dr. Leroy Nyberg and Dr. Robert Star
Date: Winter 2001-2002
The goals of this workshop are to provide (1) insights into developing a career in basic and clinical research of urologic diseases, (2) a "hands-on" experience in preparing clinical and basic research grant applications, and (3) a practical introduction to the NIH grants process. The workshop format will include interactive lectures from experts and individualized breakout sessions for practical application. Areas of emphasis are as follows:

- Funding mechanisms most applicable to beginning investigators
- Scientific method
- Successful NIH grants
- Grantsmanship—what it is and how to perfect it
- NIH review and funding process
- Revised applications—how to prepare and submit
- Networking, visibility, and quality publications—why they are necessary
- Successful competitive renewal applications

Workshop on Erythroid Lineage Genomics
Organizer: Dr. Terry Bishop
Date: Winter 2001-2002
The goals of this two-day workshop are as follows:

- Assess the current knowledge of gene expression in cells committed to erythroid differentiation
- Discuss tactics for merging the fields of computational biology with erythroid cell physiology
- Develop a research plan that will integrate functional genomics, microarray technology, proteomics, and bioinformatics with the molecular genetics and biochemistry of erythroid lineage cells at various stages of differentiation

Various experts will discuss the following items:

- Genes regulating hemoglobin production, membrane structure, and metabolism of erythroid cells
- Changing gene expression patterns during erythropoiesis
- Growth factors required for erythropoiesis and their interaction with receptors
- Exploration of the genome for erythroid-specific expressed genes
- Developing and maintaining tissue-specific databases
- State-of-the-art techniques for analyzing the function of the genome
- Systems biology

Urinary Reflux and Obstructive Uropathy in Children
Organizer: Dr. Leroy Nyberg
Date: Spring 2002
This conference aims to provide an up-to-date overview of basic and clinical knowledge of urinary reflux and obstructive uropathy in children, to determine areas where

additional basic and clinical research is needed, and to develop a research plan. To accomplish these goals, introductory plenary sessions and topic-specific breakout groups will address the following:

- Epidemiology
- Genetics
- Accuracy and effectiveness of diagnostic techniques
- Classification and grading
- Treatment strategies and outcomes
- Prognosis
- Effects on adult bladder function
- Animal models

Proteinuria and Other Markers of Progression of Kidney Disease
Organizer: Dr. Thomas Hostetter
Date: Spring 2002

Total protein or albumin excretion rates are currently the best markers of progressive renal disease, short of measurements of glomerular filtration rate (GFR) and its related parameters such as serum creatinine. However, changes in GFR and associated measures are slow to occur and can be expensive to determine. Better markers of progression of disease are needed to facilitate trials of new therapies. Topics of interest for this conference include the following:

- Relation of proteinuria to progression of disease and to therapy
- Value of newer GFR markers such as cystatin
- Status of biomarkers such as TGF-beta
- Prospects for broad proteomic or mRNA screens

The perspectives of pathophysiologists, clinical trial experts, the Food and Drug Administration, and industry will be solicited. Also, knowledge about newer techniques as applied to other diseases, such as pattern scanning for serum proteins in cancer screening, will be sought.

Genetics of Complex Traits—Application to Common Urologic Disorders
Organizer: Dr. Leroy Nyberg
Date: Summer 2002

The symposium will provide an expert overview of the genetics of complex traits, discuss the application of this knowledge to relevant urologic disorders, and develop a research agenda. Panels of experts will discuss

- Molecular genetics (animal and human studies),
- Examples of the application of genetics to common diseases with complex traits
- Urologic diseases or disorders where studies would be applicable

Symposium participants will develop of a research strategy, including applicable basic and clinical research specialties.

Progress in Polycystic Kidney Disease
Organizer: Dr. Gladys Hirschman
Date: Spring 2002

The purpose of this symposium is to identify new priorities for research in polycystic kidney disease. Panels of experts will examine the

- Molecular mechanisms for disease progression

- Progress in polycystic kidney disease imaging and utilization as a marker in disease outcome
- Role of the renal angiotensin system in polycystic kidney disease progression
- Progress in the understanding of the mechanism of recessive polycystic kidney disease

Preparing for a Clinical Research Career in Nephrology
Organizer: Dr. Robert Star
Date: September 2002
Highly trained clinical researchers are needed to capitalize on the many profound developments and discoveries in the basic sciences and to translate them to clinical settings. Unfortunately, formal training in clinical research is often fragmented, producing a workforce that is unprepared for such tasks. This two-and-a-half-day conference, co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the American Society of Nephrology, is an opportunity to learn the skills needed to establish a successful clinical research career and to effectively compete for research funding. The training program will include state-of-the-art lectures, mentored training sessions on clinical research and trial design, and a mock study section using outcomes research as an example. Attendees will be expected to participate in a journal club, to design a clinical trial, and to review applications for clinical trials in a mock study section meeting.

Trans-NIH Workshop on Recruitment of Minority and Disadvantaged Populations into Clinical Research Studies
Organizers: Dr. John Kusek and Dr. Larry Agodoa
Date: September 2002
This two-day workshop will assess the current state of knowledge regarding the best techniques to recruit minority and disadvantaged populations into clinical research studies. It will also identify areas for future research. Of particular importance will be the delineation of a research agenda using ongoing or soon-to-be implemented clinical trials and other clinical research studies. Completed and ongoing clinical research studies, including randomized clinical trials, will be examined for information on rates of recruitment, techniques producing a high yield of participants, and barriers associated with participation. The studies examined will represent a wide range of diseases, include the different ethnic and racial minority populations, and encompass groups that may be considered to have a major barrier to enrollment. Breakout sessions will discuss selected topics, and on the final day, participants will review the research agenda.

Preparing for a Research Career in Bench and Translational Nephrology
Organizers: Dr. Robert Star and Dr. Terry Bishop
Date: September 2002
Physician investigators bring to non-clinical research the goal of understanding fundamental mechanisms underlying disease; hence, they are indispensable to progress in the understanding of disease and development of therapies. However, according to a study by the American Medical Association, the number of physician scientists interested in bench research dropped precipitously between 1984 and 1999, from 23,214 physician scientists to 14,357, a decline of 4.2 percent to 1.8 percent. In addition, those physicians who do go into bench and translational research often receive incomplete training. The

goals of this workshop are to attract new investigators to nephrology and to improve the training of program participants so they can capitalize on the many profound developments and discoveries in fundamental science, translate them to clinical settings, and more effectively compete for research funding. Workshop topics will include

- Choosing a mentor
- Choosing a research topic
- New technological advances
- Translational approaches in nephrology

Participants will design a research plan and evaluate grants in a mock study section.